Stabilized beta-catenin in lung epithelial cells changes cell fate and leads to tracheal and bronchial polyposis.

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Public Summary:
In summary, stabilization of β-catenin in the lung epithelium occurs in a non-uniform pattern suggesting potential differences amongst epithelial cells that hitherto had been thought to be of similar or identical developmental history. Excess β-catenin has both direct and paracrine effects on cell fate determination and differentiation. Finally, β-catenin gain-of-function using the cre-loxP system reflects both increased protein as well as mRNA. These observations should help elucidate the functional role of Wnt/β-catenin signaling during mammalian development

Scientific Abstract:
The precise mechanisms by which beta-catenin controls morphogenesis and cell differentiation remain largely unknown. Using embryonic lung development as a model, we deleted exon 3 of beta-catenin via Nkx2.1-cre in the Catnb[+/lox(ex3)] mice and studied its impact on epithelial morphogenesis. Robust selective accumulation of truncated, stabilized beta-catenin was found in Nkx2.1-cre;Catnb[+/lox(ex3)] lungs that were associated with the formation of polyp-like structures in the trachea and main-stem bronchi. Characterization of polyps suggests that accumulated beta-catenin impacts epithelial morphogenesis in at least two ways. "Intracellular" accumulation of beta-catenin blocked differentiation of spatially-appropriate airway epithelial cell types, Clara cells, ciliated cells and basal cells, and activated UCHL1, a marker for pulmonary neuroendocrine cells. There was also evidence for a "paracrine" impact of beta-catenin accumulation, potentially mediated via activation of Bmp4 that inhibited Clara and ciliated, but not basal cell differentiation. Thus, excess beta-catenin can alter cell fate determination by both direct and paracrine mechanisms.